Antimalaria Effect of Chloroquin - Sambiloto  
*(Andrographis paniculata nees)* Combination Compared with  
Chloroquin Alone In Adult Patients of Uncomplicated Malaria  
Falciparum

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INTRODUCTION

Malaria is still a major health consideration, especially in tropical countries. The prevalence rate remains high in spite of eradication efforts that are kept being done. There are some eradicating problems due to the resistance of vectors to insecticides and the parasites to antimalaria drugs (1). It was reported in Indonesia from the data of 1996 that the number of population risk to malaria was 100, with the incidence for malaria falciparum was 65.9%. Maliometric survey of priority areas outside Java-Bali within 1989 to 1997 shows parasite rate (PR) 4-5%. The data from Sub Division of Malaria Prevention of Health Dept shows that the number of malaria cases outside Java-Bali in 1997 is 1,325,633 and in North Sumatera is 49,833 in the same year (2).

North Sumatera is a province with some endemic districts, such as Nias, Tapanuli Tengah, Tapanuli Selatan, Langkat, Asahan, Labuhan Batu, Deli Serdang, and Mandailing Natal (Madina). The latest has been considered by Health Dept. of Indonesia to be a district resistant to Chloroquin (not uniform distribution) since 1994. Tropical and Infective Medicine Division of Internal Medicine of Medical School, University of Sumatera Utara (USU) have conducted some researches in this district. Ginting, et al (4) in 2001 found the resistance to Chloroquin was 47.5% and to Sulfadoxyn-Pyrimethamine was 50% in vivo. It is demanded to find other antimalaria drugs whose potency can be improved, due to the lack of antimalaria available in Indonesia. Resistance acceleration of *Plasmodium falciparum* to Chloroquin and Sulfadoxyn-Pyrimethamine becomes a greater threat in Indonesia, especially in North Sumatera.

Sambiloto herb (*Andrographis paniculata nees*) is one of medicine plants available over Indonesia with various local names. Javanese has already known this multi branched-
bush as a potent drug for snake poisons since old time \(^6\). In Sumatera it is known as *Pepaitan*, in Java as *Sambilata, Takila, Bidara, Sadilata, Ki oray, Ki peurat*, and *Ki ular*. In Chinese it is called *Chuan xin lian*\(^7\).

*Andrographis paniculata* (AP), which is also known as “King of Bitters”, is a plant from family *Acanthaceae* that has been used for centuries in Asia to treat digestive and respiratory diseases, fever, herpes, throat infection, and many other chronic and infection diseases, including malaria. It was found in Indian Pharmacopoeia and has been written in at least 26 Ayurvedic formulas. In Traditional Chinese Medicine (TCM), AP has an important role as a “cold property” and used as antipyretic agent, it also cleans poisons within the body. Pharmacologically AP is considered as analgesic, anti-inflammatory, antibacterial, antiperiodic (as in malaria), antiviral, vermicide, and immunity improving agents (improve leukocyte phagocytose, inhibit HIV virus replication, increasing the number of CD4+ and T lymphocytes) \(^5\).

The clinical study of the herb to cure patients of malaria has not yet been found. Considering the literatures above we find it is reasonable to examine the effectiveness of sambiloto extract to adult patients of uncomplicated malaria falciparum. The dose of simplicia for adults is distributed among 1,000 – 2,000 mg daily for 3 – 5 days \(^10, 16\). The dose of dried leafs to cure many kinds of infections is 10 – 15 g daily \(^17\).

From the study of *Lethal Dose* (LD\(_{50}\)) in mice, AP is known has low toxicity, which is 1,800-mg/kg-body weight.\(^{18}\)

**REQUIREMENTS AND METHOD**

The study is clinically examination method, using double blind parallel design. The clinical result is determined based on the effects occurred in Chloroquin-Sambiloto group (QS) compared with Chloroquin control group (C).

**Study Population**
The populations are patients administered to Panyabungan General Hospital, Mandailing Natal District, North Sumatera.

Sample included:
1. Adult male and female
2. Performs clinical and laboratory signs of malaria falciparum without any complications
3. Not during pregnancy nor lactacy
4. Informed concern

Sample excluded:
1. Parasitologically proved other plasmodiums than falciparum alone
2. Having Chloroquin treatment 2 weeks before the study, found by interview and Dill & Glazko test in urine
3. Low compliance
4. Immunosensitive to Chloroquin and Sambiloto
5. Clinically worsen, or parasite account in the third day is stable or even increased
6. Taking antibiotics and/antipyretics
7. Not getting controlled

**Study Design**

All patients met requirement criteria were clinically assessed completely, including by taking history of illness (anamnesis) and doing physical diagnostic. Routine laboratory assessment was done, as well as malaria blood smear, both thick and thin film, stained with Giemsa 10% and examined microscopically to find asexual forms of *Plasmodium falciparum*. Parasite account was done in day 0 to 7, and day 14 in the hospital laboratory. Oral temperature was checked every 6 hours until the fever was over.

Sambiloto given in simplicia form was extracted with ethanol in Pharmacy laboratory of Mathematic and Science Faculty, USU. The simplicia is placed in capsules of form and color resembled to placebo given to control group.

The chloroquin dose was 600 mg base (4 tablets) in the first day, and 300 mg (2 tablets) after the next 6 hours. In the second and third day was 300 mg (2 tablets) each. Total chloroquin dose was 1,500 mg base. The sambiloto dose was 250 mg simplicia (1 capsule) three-divided dosage for 5 alternate days, as well as placebo capsules.

Chloroquin and Chloroquin-Sambiloto were randomly given to patients who met criteria. They were followed during the study to assess compliance, adverse effects, complications, and other important clinical responses. If the patients were found to have complications or perform severe malaria or parasite account was not less or even increased within 3 days, they would be given intensive care immediately by giving quinine sulphate drips, and excluded from the study.

**Early Treatment Failure (ETF)** of Chloroquin is determined by (19):

1. Finding alarmed signs or severe malaria with complication in D1, D2, D3, and parasitemia level is ≥ 5%
2. Parasite account in D2 > D1
3. Parasite account in D3 ≥ 25% D0

All patients were hospitalized during the study. Student T Test and Chi-square analyzed the statistic by using SPSS 10.0 computer program, and significant value determined for p < 0.05.

**RESULT**

**Characteristics of Study Subjects**

The study was held from April to June 2003 to patients of uncomplicated malaria falciparum, hospitalized in Panyabungan General Hospital. All 120 patients who met criteria were randomized to receive Chloroquin-Placebo (C) or Chloroquin-Sambiloto
There were 58 patients in C group and 62 in CS group. During the study, 8 patients were excluded from C group due to these conditions: not getting controlled (3), performed adverse effect of drug such as nausea and vomiting (2), worsen condition or severe malaria (2), and low compliance (1). There were 6 patients excluded from CS group due to not getting controlled (4) and low compliance (2). In the end of the study, there were 50 in C group and 56 in CS group (table 1).

Table 1: Demography Data in C and CS Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Age (Year) Mean</th>
<th>Sex</th>
<th>BW(kg) Mean</th>
<th>BH(cm) Mean</th>
<th>Temp 0°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquin</td>
<td>39,06</td>
<td>♂ 21</td>
<td>29</td>
<td>55,58</td>
<td>159,98</td>
</tr>
<tr>
<td>Chloroquin-Sambiloto</td>
<td>37,30</td>
<td>♂ 25</td>
<td>31</td>
<td>54,36</td>
<td>159,05</td>
</tr>
</tbody>
</table>

The most common complaints over all patients were headache (91.5%), whilst fever was only found in 32% patients (table 2).

Table 2: Complaints of Patients of Uncomplicated Malaria Falciparum

<table>
<thead>
<tr>
<th>Complaints</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>97</td>
<td>91,5</td>
</tr>
<tr>
<td>Myalgia</td>
<td>86</td>
<td>81,1</td>
</tr>
<tr>
<td>Nausea</td>
<td>53</td>
<td>50,0</td>
</tr>
<tr>
<td>Back pain</td>
<td>52</td>
<td>49,0</td>
</tr>
<tr>
<td>Fever</td>
<td>34</td>
<td>32,0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>18,8</td>
</tr>
<tr>
<td>Shivering</td>
<td>15</td>
<td>14,1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>5,6</td>
</tr>
</tbody>
</table>

Chi Square statistical study gave significant value of effectiveness of both group (p<0.05). *Plasmodium falciparum* resistant to Chloroquin was 48% and resistant to Chloroquin-Sambiloto was 12.5%.

Complaint of fever in both treatment group was only 34 over 106 patients (32%) with approximate body temperature 37,3°C, and most of them were sub febril. There were no significant correlations between the fever and parasite account in peripheral blood smear (r<0.25). Fever Clearace Test could not be analyzed to both treatment group.

We evaluated the clearance of parasites through blood film examination (Parasite Clearance Test/PCT) in day 1 (D1), day 2 (D2), day 3 (D3), day 7 (D7), and day 14 (D14) after treatment. The PCT value of each group using Chi square statistic, is listed in table 4.
Tabel 4: Parasite Clearance Time in Both Group of Uncomplicated Malaria Falciparum

<table>
<thead>
<tr>
<th>PCT</th>
<th>Treatment Group</th>
<th>Chloroquin</th>
<th>Chloroquin-Sambiloto</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2</td>
<td></td>
<td>1</td>
<td>5</td>
<td>0,000</td>
</tr>
<tr>
<td>H3</td>
<td></td>
<td>6</td>
<td>13</td>
<td>0,000</td>
</tr>
<tr>
<td>H7</td>
<td></td>
<td>17</td>
<td>25</td>
<td>0,071</td>
</tr>
<tr>
<td>H14</td>
<td></td>
<td>26</td>
<td>43</td>
<td>0,02</td>
</tr>
</tbody>
</table>

PCT value in D2 and D3 of Chloroquin-Sambiloto group was higher than the other group, and statistically significant (p=0.000). PCT in D7 was salo higher in the CS group, but statistically not significant (p=0.071). PCT in D14 was significantly different in both group (p=0.02).

The decrease of parasitemia level in CS group was lower and occured since D2 to D14 (Figure 1). Parasitemia level in both group significantly different in T Test (p<0.05).

Figure 1: Parasitemia Decreasing Level of C and CS Patients (data shown Mean ± SD)

DISCUSSION

*Andrographis paniculata* is a species of family Acanthacea, which is a family of multi branched plants measure up to 90 cm in height, whose branches is square. The leaf is small and lancet-like, flat branched, dark green colored, and plain edge (no zigzags). The flower is yellowish white. The fruit is small cone-shape; the mature ones will be torn to
form 4 sheaths. It grows in tropical areas in up to 700 m altitude; the favorable condition is open air and rich soil.

Sambiloto contains many kinds of useful ingredients, such as: *Andrographolidae* which is the highest concentration in leaf (2.39%), Diterpenoids viz, Deoxyandrographlide, -19β-D-glucoside, *Neo andrographolide*, homoandrographolide, andrographine, paniculide A, B, and C, paniculine, calmagenin, and kalium. It is absorbed and excreted rapidly. Eighty percent of excretion occurs in kidney (urinary tract) and digestive tract, 90% will be eliminated within 48 hours.

One study of antimalaria effect of sambiloto which has been reported is carried out by Widyawaruyanti et al. (1995) in Kuala Lumpur compared antimalaria effect of AP with 2 other kinds of herb (*Piper sarmentosum* and *Tinospora crispa*), and found that antimalaria effect of AP in vivo is higher, and the chloroform extract inhibits the growth of parasite in vitro in lower dose than methanol extract.

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Thamlikitkul, et al. (10) carried out clinical test of anti-inflammatory effect of AP in adult patients of pharyngotonsilitis, and found that high dose of AP has significant effect of curing fever and throat burn sensation in day 3, compared with low dose AP.

Caceres, et al. (11) compared AP extract 1200 mg daily with placebo to common cold patients; found that AP has better effectiveness and no adverse effect.

Melchior, et al. (12) carried out a phase III clinical study to patients of upper respiratory tract infection without complication and found a significant recovery from AP group compared with placebo.

Fever is not a major complaint of malaria falciparum patients. This is a common phenomenon in endemic area due to particular immunity formed during reinfection, which decreases body response to the plasmoidium infection. Patients showed normal temperature were 18 and 16 in chloroquin and chloroquin-sambiloto group, respectively.

Patients whose plasmoidium sensitive to chloroquin-sambiloto were more than those to chloroquin alone, and it was statistically significant (p<0.05). It shows that the addition of sambiloto in chloroquin therapy of patients of uncomplicated malaria falciparum may increase plasmoidium sensitivity.

The spreading acceleration of plasmoidium to antimalaria drugs is not equal in every area or country. According to White (19), there are three factors produce resistance, i.e. operational, pharmacological, and malaria transmission factors. Operational factors are sub therapeutic dose and low compliance of patients. Malaria transmission factor
included intensity, drug pressure, and immunity. Rational combination therapy is strongly recommended to inhibit or lowering the acceleration. WHO in 2001 recommend the combination of conventional therapy with Artemycin in endemic areas.

Chloroquin resistance in Indonesia is not as high as in other countries such as Thailand and Vietnam, yet we need early anticipation before it becomes a severe problem. Herb plants such as sambiloto has undergone various examinations abroad. Though it has never been examined to malaria patients, it has effect to plasmodium in vitro. Yet it has been widely used as phytopharmacy for malaria. Considering all of the reasons, we need to examine the efficacy of chloroquin with sambiloto, since it is available in Indonesia, especially in North Sumatera.

Since chloroquin is available and a cheap conventional antimalaria, and the resistance is 48%, a new regime is demanded to overcome the resistance problem. Sambiloto seems to be a phytopharmacy used for a long time in Indonesia to cure many kinds of symptoms, yet the safety has been proven, it can be combined with chloroquin or other antimalaria to increase the parasite sensitivity to drugs or as an anti resistance that still needs further examination. According to WHO recommendation (20), combination therapy in malaria falciparum is important to inhibit the resistance acceleration of the plasmodium to various antimalaria drugs.

SUMMARY

1. Malaria is still an important health problem in Indonesia, including in Mandailing Natal District of North Sumatera
2. It is demanded to find alternative regime of antimalaria, since the development of the drugs is not equivalent to resistance acceleration of plasmodium to various preparations
3. Resistance value is 48% and 12.5% of Plasmodium falciparum to chloroquin and chloroquin-sambiloto, respectively
4. Indonesia traditional herb medicines need to be improved, especially those with antimalaria effect, to overcome the lack of antimalaria drugs
5. Sambiloto herbs in simplicia capsule administered tid 250 mg for 5 days is proven to increase sensitivity level of plasmodium
6. Further study is demanded, that is to combine sambiloto with other antimalaria drugs, as well as clinical study of the herb alone to confirm the effectiveness to Plasmodium falciparum

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